REMARKS

Claims 1-4, 7-8, 11, and 14-59, as amended are pending in this application for the Examiner's review and consideration. New claims 59-67 have been added. Applicants note that the Examiner indicates that only claims 1-4, 7-8, and 14-58 are pending in this application. Claim 11, however, is also currently pending (*See, e.g.*, Preliminary Amendment filed October 29, 2001)

The specification was amended to correct an obvious typographical error pointed out by the Examiner. Specifically, the specification was amended to correct a typographical error wherein Applicant inadvertently stated at page 3, lines 2-3 "when B_1 is H and Y is OH, H they can form a six-membered ring ketal or acetal." Applicants have corrected this passage to properly recite --when B_1 is OH and Y is OH, H they can form a six-membered ring ketal or acetal--. Applicants note that B_1 cannot be H but must be OH, *i.e.*, OR_{24} wherein R_{24} is H (*See, e.g.*, Specification, page 3, line 1 and 10-11). Indeed, each of the reaction Schemes and Examples in the specification show compounds wherein B_1 is OH. Furthermore, one skilled in the art would readily recognize that a ring ketal or acetal could only be formed if B_1 was an OH group.

Claim 1 was amended to recite that the 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur can be saturated or unsaturated (*See, e.g.*, Specification, page 5, lines 27-29). Claim 1 was also amended to recite that the cycloalkyl group of R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{15}, R_{23}, and R_{29} contains 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring (*See, e.g.*, Specification, page 19, lines19-22). Finally, claim 1 was amended to particularly point out and distinctly claim "heterocyclo" in two occurrences as --a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur-- so that heterocyclo is consistent with the definition for heterocyclo used earlier in the claim (*See*, amendment filed October 29, 2001). Claim 14 was amended to be written in independent form. Claims 4, 8, 11, 15, 23, 25, 27, and 29 were amended to simply replace the phrase "ovary cancer" with --ovarian cancer--.

New claims 59-67 have been added (*See, e.g.*, Specification, page 1, line 1 to page 2, line 18; page 8, line 20 to page 9, line 11; and page 10, line 10 to page 11, line12). No new matter has been added by these claim amendments or the new claim so that their entry at this time is warranted. No fee is believed to be due for these amendments.

Furthermore, a large number of decisions have held that terms like "substituted alkyl" and "substituted aryl" pass muster under 35 U.S.C. § 112, second paragraph. For example, in *Ex parte Lewis et al.*, 197 U.S.P.Q. 543 (Bd. Pat. App. & Inter. 1977), the claim term "substituted alkyl" was found definite *(See also, Ex parte Breuer*, 1 U.S.P.Q.2d 1906 (Bd. Pat. App. & Inter. 1986) (the claim terms "substituted aryl", "substituted alkyl", and "heterocycles" are definite); *Cf. Ex parte Takeyama et al.*, 2000 WL 33149253 (Bd. Pat. App. & Inter. 2000). In *Ex parte Lewis et al.* claim 1 as issued in the corresponding patent, 4,105,431, reads as follows:

> A composition for inhibiting the growth of bacteria, fungi, or algae comprising an agronomically-acceptable carrier and, in an amount which is effective to adversely affect the growth of bacteria, fungi, or algae, a compound of the formula . . . wherein Y is an unsubstituted or substituted alkyl, alkenyl, or alkynyl group of 1 to 18 carbon atoms, an unsubstituted or substituted cycloalkyl group having a 3 to 6 carbon atom ring and up to 12 carbon atoms, an unsubstituted or substituted aralkyl group of up to10 carbon atoms, or an unsubstituted or substituted aryl group of up to 10 carbon atoms.

The Examiner rejected what eventually became issued claim 1 under 35 U.S.C. § 112, second paragraph, stating that the term "substituted" rendered the claim too broad and indefinite. The Board reversed stating that the specification adequately teaches how to make and use the compounds and that the term is definite when read in view of the specification.[1] Importantly, Applicants note that the definitions provided in *Ex Parte Lewis et al.* to define substituted alkyl groups and substituted aryl groups are analogous to the definitions used in the present application. Applicants respectfully submit that the term "substituted" does not render independent claim 1 or claims that depend therefrom indefinite. Withdrawl of this rejection is respectfully requested.

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[1] The terms were defined in the specification of the application at issue in *In Ex Parte Lewis et al.* as follows:

substituted alkyl groups . . . include hydroxyalkyl, haloalkyl, cyanoalkyl, alkylaminoalkyl, dialkylaminoalkyl, arylaminoalkyl, carboxyalkyl, carbalkoxyalkyl, alkoxyalkyl, aryloxyalkyl, alkylthioalkyl, arylthioalkyl, haloalkoxyalkyl, cycloalkylaminoalkyl, such as morpholinoalkyl, piperidinoalkyl, pyrrolidonylalkyl, and the like, carbamoxyalkyl, alkenyl, haloalkenyl, alkynyl, haloalkynyl, isothiazolonylalkyl, and the like.

By a substituted aryl group is meant an aryl group, such as benzene, naphthalene, or pyridine, having one or more of the hydrogen atoms on the aryl ring replaced by another substituent group. Examples of such substituent groups include halogen, nitro, lower alkyl, lower alkylacylamino, lower carbalkoxy, sulfamyl, and the like.

Applicants wish to thank the Examiner for pointing out the typographical error concerning the definition of B_1 in the phrase "when B_1 is H and Y is OH, H, they can form a six membered ring ketal or acetal." Applicants have amended claim 1 to properly recite --when B_1 is OH and Y is OH, H they can form a six-membered ring ketal or acetal--.

The Examiner further alleges that it is not clear if a saturated or unsaturated ring system is called for the group G. The specification, however, clearly states that the heterocycle ring system is a saturated or unsaturated ring system (*See, e.g.*, Specification, page 5, lines 27-29). Since the claims are read in light of the specification, one of ordinary skill in the art would readily understand that the phrase a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur includes saturated and unsaturated ring sytems. Applicants, however, have amended claim 1 to specifically recite "a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur." Thus, withdrawl of this rejection is respectfully requested.

The Examiner further alleges that the term "cycloalkyl" is indefinite because it is not known how many atoms make up the ring and what kind of ring is intended. Again, Applicants note that the claims are read in light of the specification and the specification clearly states that:

> The term "cycloalkyl" refers to optionally substituted, saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring.

Thus, one of ordinary skill in the art would readily recognize that the term "cycloalkyl" includes 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring. Applicants, however, have amended claim 1 to clearly recite these features.

The Examiner also alleges that the phrase "and pharmaceutically acceptable salts thereof and" should be written using the word "or" to place it in the alternative form. In response, Applicants have amended claim 1 to place it in the alternative form.

The Examiner alleges that it is unclear in claim 39 which additional anti-cancer agent is intended. Claim 39 depends from claim 4 and recites that an additional anti-cancer agent is administered with the compound of claim 1 to treat the cancers recited in claim 4. Applicants respectfully submit that any known anti-cancer agent can be used as the additional anti-cancer agent in

the combination therapy recited in claim 39 (*See, e.g.*, Specification, page 10, lines 10-12). Other anti-cancer agents are well known to those of ordinary skill in the art and one of ordinary skill in the art would readily be able to identify what other anti-cancer agent(s) could be administered with the compounds of the invention to treat the recited cancers. Indeed, the specification recites preferred additional anti-cancer agents (*See, e.g.*, Specification, page 10, lines 18-29) that can be administered with the compounds of the invention to treat the cancers recited in claim 4. These preferred additional anti-cancer agents are specifically recited in claims 40-41. For the above reasons, Applicants respectfully submit that claims 1-4, 7-8, and 14-58 are not indefinite. Accordingly Applicants respectfully request that the rejection of these claims under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

RESPONSE TO ELECTION AND COMMENTS ON PROVISO

Concerning the Examiner's request that Applicants point out compounds in the prior art that are excluded by the proviso of claim 1, Applicants respectfully submit that the epothilone art is well known and that Applicants have met their duty of disclosure by providing to the United States Patent and Trademark Office copies of the references that Applicants are presently aware of. However, to expedite prosecution and for the Examiner's convenience, Applicants point out that the proviso excludes epothilones A, B, C, D, and E.

Concerning the Examiner's request that Applicants elect a single species, Applicants elect the compound of Example 3, claim 14. Finally, Applicants respectfully submit that claim 1 is searchable; however, they have complied with the Examiner's species election.

CONCLUSION

Applicants believe the application is in condition for allowance and earnestly requests reconsideration of the claims and allowance thereof. If the Examiner has any questions or suggestions to expedite allowance of this application, however, the Examiner is respectfully invited to call the undersigned to discuss the matter further.

An amendment fee of $246 is believed to be due for this submission for the addition of 1 independent claim in excess of 3 and 9 dependent claims. Please charge the fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Paul E Dietz (45,627)

Date: March 4, 2002

for Anthony M Insogna 35,203

Anthony M. Insogna (Reg. No.)

PENNIE & EDMONDS LLP
1667 K Street , N.W.
Washington, DC 20006
(202) 496-4460

Appendix A

Changes to the Specification for Application No. 09/084,542; filed May 26, 1998

The paragraph at page 3, line 1 to page 3, line 3 is revised as follows:

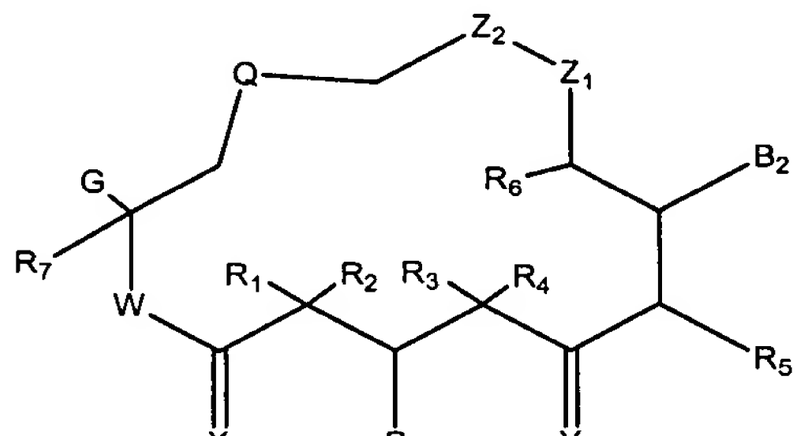
-- B_1 and B_2 are selected from the group consisting of OR_{24}, or $OCOR_{25}$, or $O_2CNR_{26}R_{27}$; when B_1 is OH and Y is OH, H they can form a six-membered ring ketal or acetal;--

Appendix B

Changes to the claims for Application No. 09/084,542; filed May 26, 1998

The claims were revised as follows:

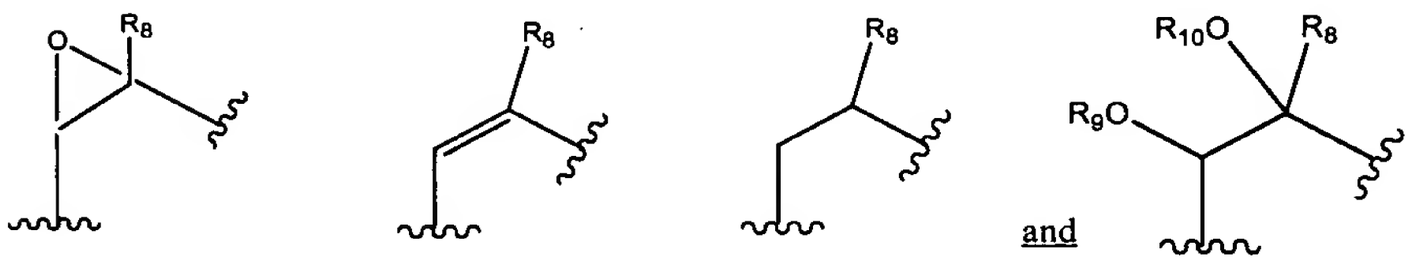
1. (Fourth amendment) A compound of the formula:



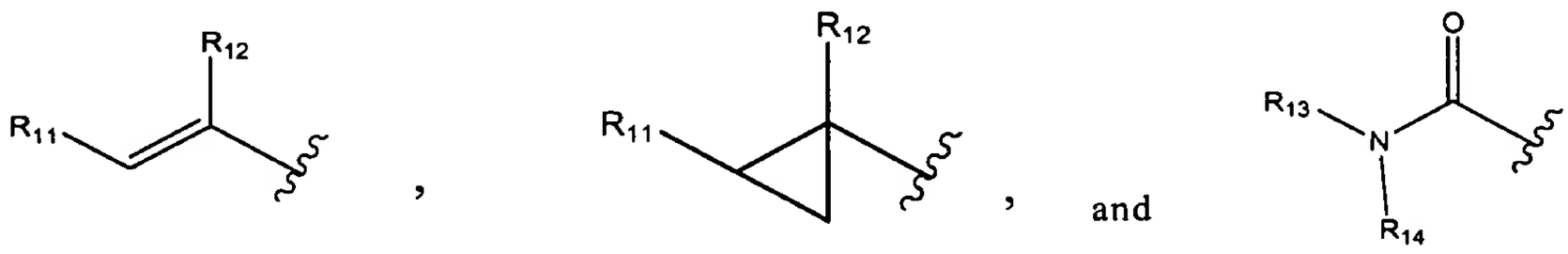
V

wherein:

Q is selected from the group consisting of:



G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H;[,] alkyl;[,] substituted alkyl;[,] aryl;[,] substituted aryl;[,] cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and [heterocyclo] a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H;[,] alkyl;[,] substituted alkyl;[,] aryl;[,] substituted aryl;[,] cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; [heterocyclo,] a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated, ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C$=O;[,] $R_{33}SO_2$;[,] hydroxy;[,] O-alkyl or O-substituted alkyl; [and

the] or pharmaceutically acceptable salts [thereof and any], hydrates, solvates or geometric, optical [and] or steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

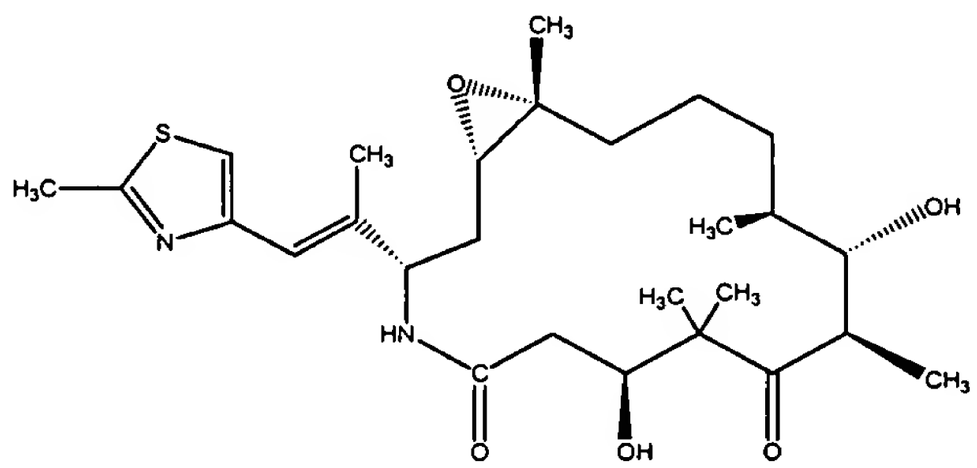
are excluded.

4. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

8. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

11. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

14. (Amended) A [The] compound [of claim 1] having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer[,] optical isomer, or stereoisomer thereof.

15. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient

in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

23. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

25. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

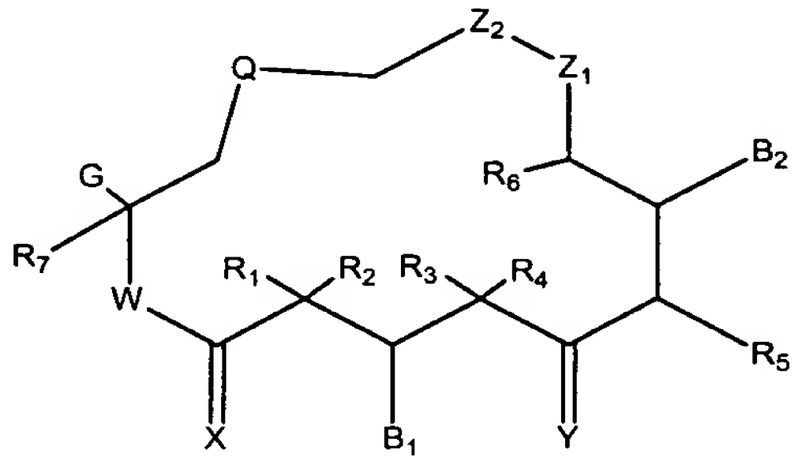
27. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

29. (Amended) A method of treating breast cancer, [ovary] ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

Appendix C

Pending claims for Application No. 09/084,542; filed May 26, 1998

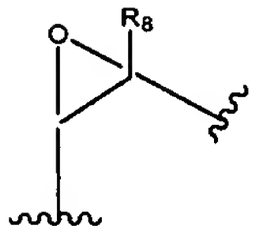
1. A compound of the formula:

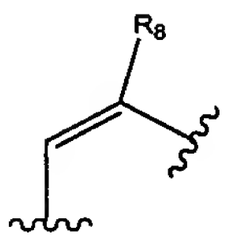


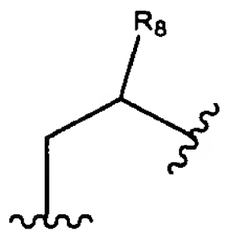
V

wherein:

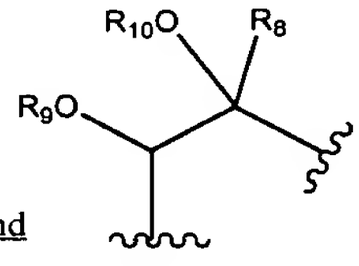
Q is selected from the group consisting of:



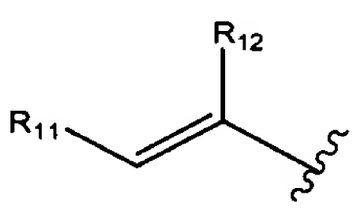




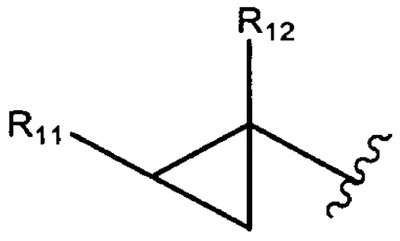
and



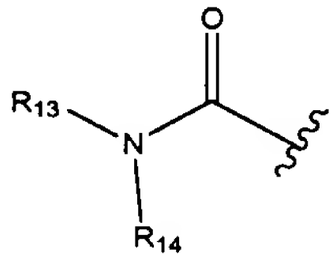
G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



,



, and



W is O or NR_{15};

X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and

O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C=O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof;

with the proviso that compounds wherein

W and X are both O; and

R_1, R_2 and R_7 are H; and

R_3, R_4 and R_6 are methyl; and

R_8 is H or methyl; and

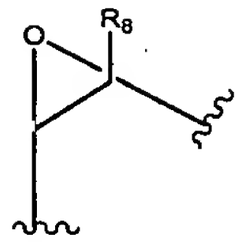
G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

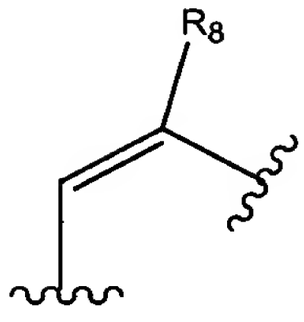
Q is as defined above

are excluded.

2. The compound of claim 1 wherein

Q is





X is 0;

Y is 0;

Z_1, and Z_2, are CH_2 and

W is NR_{15}.

3. A compound selected from the group consisting of:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[l-methyl-2-(2-methyl--4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

e

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-tetramethyl-16-[l-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-]l-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)etheny]]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[4.10]heptadecane-5,9-dione;

[4S-[4R*-7S*,8R,*9R-,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl-1-aza-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl)-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,BR*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazoly)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,(E)]]-4,8-Dihydroxy,5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazoly)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydxocymethy1-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;
and the pharmaceutically acceptable salts, solvates and hydrates thereof.

4. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal

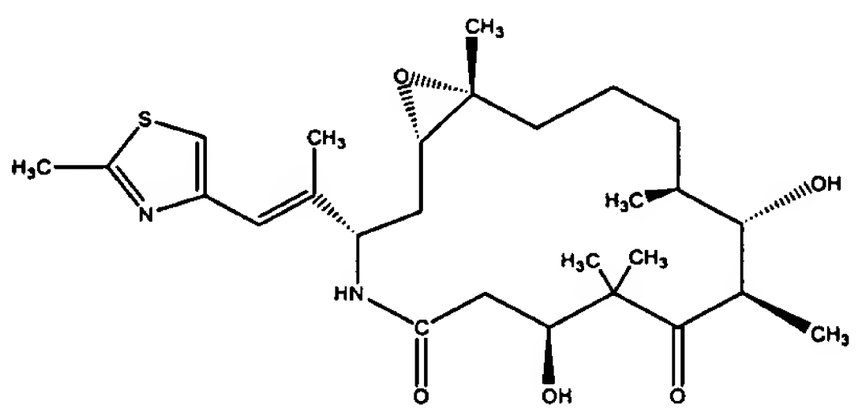
cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

7. The method of claim 4, wherein the cancer is cancer of the breast, ovary, or colon.

8. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

11. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

14. A compound having the formula:



or a pharmaceutically acceptable salt, hydrate, solvate, geometrical isomer, optical isomer or stereoisomer thereof.

15. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment

which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

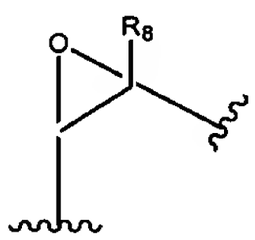
16. The method of claim 15, wherein the cancer is cancer of the breast, ovary, or colon.

17. The method of claim 8, wherein the cancer is cancer of the breast, ovary, or colon.

18. The method of claim 11, wherein the cancer is cancer of the breast, ovary, or colon.

19. The compound of claim 1, wherein G is 1-methyl-2-(substituted-4-thiazolyl) ethenyl group.

20. The compound of claim 1, wherein Q is



21. The compound of claim 1, wherein W is NR_{15}.

22. The compound of claim 1, wherein X and Y are each O.

23. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

24. The method of claim 23, wherein the cancer is cancer of the breast, ovary, or colon.

25. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

26. The method of claim 25, wherein the cancer is cancer of the breast, ovary, or colon.

27. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

28. The method of claim 27, wherein the cancer is cancer of the breast, ovary, or colon.

29. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

30. The method of claim 29, wherein the cancer is cancer of the breast, ovary, or colon.

31. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

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32. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 2.

33. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 3.

34. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 14.

35. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 19.

36. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 20.

37. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 21.

38. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 22.

39. The method of claim 4, further comprising administering one or more of a additional anti-cancer agent.

40. The method of claim 39, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

41. The method of claim 40, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

42. The method of claim 4, further comprising administering radiation therapy.

43. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable vehicle or diluent.

44. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable vehicle or diluent.

45. A pharmaceutical composition comprising the compound of claim 3 and a pharmaceutically acceptable vehicle or diluent.

46. A pharmaceutical composition comprising the compound of claim 14 and a pharmaceutically acceptable vehicle or diluent.

47. A pharmaceutical composition comprising the compound of claim 19 and a pharmaceutically acceptable vehicle or diluent.

48. A pharmaceutical composition comprising the compound of claim 20 and a pharmaceutically acceptable vehicle or diluent.

49. A pharmaceutical composition comprising the compound of claim 21 and a pharmaceutically acceptable vehicle or diluent.

50. A pharmaceutical composition comprising the compound of claim 22 and a pharmaceutically acceptable vehicle or diluent.

51. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 1.

52. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 2.

53. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 3.

54. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 14.

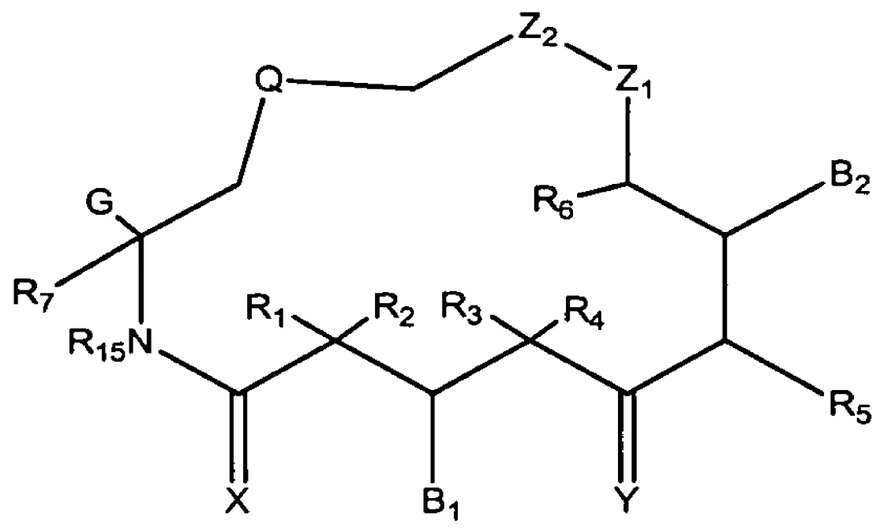
55. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 19.

56. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 20.

57. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 21.

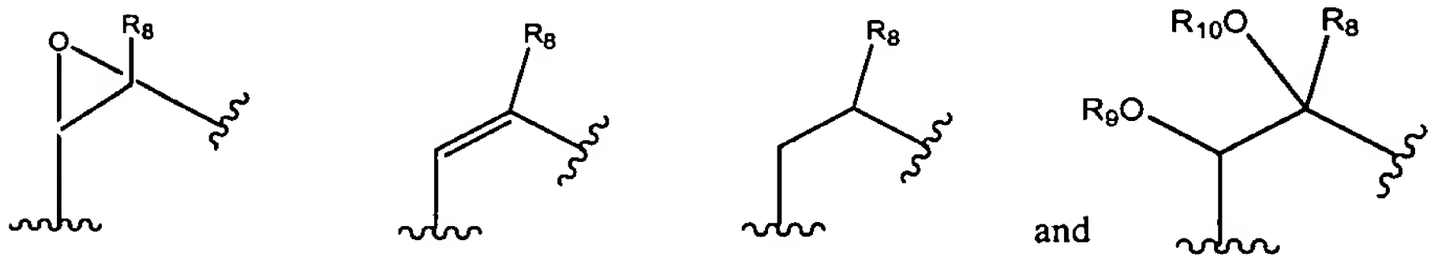
58. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 22.

59. A compound of the formula:

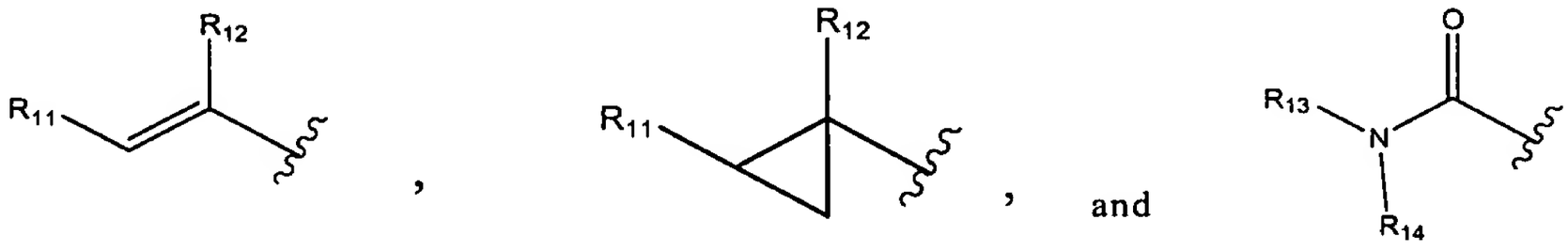


wherein:

Q is selected from the group consisting of:



G is selected from the group consisting of alkyl; substituted alkyl; substituted aryl; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;



X is O or H, H;

Y is selected from the group consisting of O; H, OR_{16}; OR_{17}, OR_{17}; NOR_{18}; H, NOR_{19}; H, $NR_{20}R_{21}$; H, H; and CHR_{22}; wherein OR_{17}, OR_{17} can be a cyclic ketal;

Z_1 and Z_2 are independently CH_2;

B_1 and B_2 are independently selected from the group consisting of OR_{24}, $OCOR_{25}$, and O-C(=O)-$NR_{26}R_{27}$, and when B_1 is OH and Y is OH, H, they can form a six-membered ring ketal or acetal;

R_1, R_2, R_3, R_4, R_5, R_7, R_{13}, R_{14}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26} and R_{27} are selected from the group consisting of H, alkyl, substituted alkyl, and aryl, and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl, and when R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_6 is methyl;

R_9, R_{10}, R_{16}, R_{17}, R_{24}, R_{25} and R_{31} are selected from the group consisting of H, alkyl, and substituted alkyl;

R_{11}, R_{12}, R_{28}, R_{30}, R_{32}, and R_{33} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; and a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

R_8 is hydrogen or methyl;

R_{15}, R_{23} and R_{29} are selected from the group consisting of H; alkyl; substituted alkyl; aryl; substituted aryl; cycloalkyl containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C_3-C_7 carbocyclic ring; a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic saturated or unsaturated ring system having between 1 and 3 heteroatoms selected from nitrogen, oxygen, and sulfur; $R_{32}C{=}O$; $R_{33}SO_2$; hydroxy; O-alkyl or O-substituted alkyl;

or pharmaceutically acceptable salts, hydrates, solvates or geometric, optical or steroisomers thereof.

60. A method of treating breast cancer, ovarian cancer, colon cancer, head and neck cancer, lung cancer, gynecological cancers, brain cancer, germ cell cancer, urothelial cancer, esophageal cancer, prostrate cancer, bladder cancer, or pancreatic cancer in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.

61. The method of claim 60, wherein the cancer is cancer of the breast, ovary, or colon.

62. A method of treating a cancer responsive to microtubule stabilization in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 59.

63. The method of claim 60, further comprising administering one or more of a additional anti-cancer agent.

64. The method of claim 63, wherein the additional anti-cancer agent acts in a phase of the cell cycle other than the G_2-M phase.

65. The method of claim 64, wherein the additional anti-cancer is a thymidilate synthase inhibitor, a DNA cross linking agent, a topoisomerase I or II inhibitor, a DNA alkylating agent, a ribonuclase reductase inhibitor, a cytotoxic factor, or a growth factor inhibitor.

66. A method of treating melanoma, non-Hodgkin's lymphoma, multiple myeloma, or Karposi's sarcoma in a patient in need of said treatment which comprises administering to said patient a therapeutically effective amount of a compound of claim 59.

67. A pharmaceutical composition comprising the compound of claim 59 and a pharmaceutically acceptable vehicle or diluent.